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RECD 27 JUL 2004
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AFB/JAS/P9642WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/02911	International filing date *(day/month/year)* 04.07.2003	Priority date *(day/month/year)* 05.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K9/50		
Applicant TEMREL INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.12.2003	26.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Merkl, B Telephone No. +49 89 2399-2138

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/02911

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-8, 10-34	as originally filed
9, 9a	filed with telefax on 01.06.2004

Claims, Numbers

1-38	filed with telefax on 01.06.2004

Drawings, Sheets

1/6-6/6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 19-24, 30-35

   because:

   ☒ the said international application, or the said claims Nos. 19-24, 30-35 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-38
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-38
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18,25-29,36-38 (see separate sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

Item III: For the assessment of the present claims 19-24, 30-35 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Rule 67.1(iv) PCT, Article 34(4)(a)(i) PCT).

Item V:

1. D1: US-A-5 260 069 (CHIH-MING CHEN) 9 November 1993 (1993-11-09)
   D2: US-A-5 834 024 (GRANT WAYNE HEINICKE; ET AL.) 10 November 1998 (1998-11-10)
   D3: US-B1-6 267 990 (WILFRIED FISCHER; ET AL.) 31 July 2001 (2001-07-31)
   D4: US-A-5 834 021 (CHRISTOPHER J. SPEIRS) 10 November 1998 (1998-11-10)
   D5: WO 97 02020 A (BYK GULDEN LOMBERG) 23 January 1997 (1997-01-23)

2. D1 discloses tablets comprising several polulations of pellets coated with different thickness of a coating composition comprising Eudragit S100 (see e.g. Example 1). Said coatings give different lag times which means that the release takes place at different locations during the transport through the intestines.

   D2 discloses a blend of long lag and short lag pellets comprising a drug and where the thickness of the coating layer surrounding the long lag pellet is greater than the one surrounding the short pellet. The coating can be Eudragit L or S.

   D3 discloses a preparation comprising 3 kinds of pellets, 2 of them coated with a different amount of Eudragit S 100 (see Examples) to form first and second delayed release pellets.

3. D1 and D2 disclose pharmaceutical compositions in which different pluralities of

pellets are coated with different thickness of a blended polymer mixture. According to the applicant said coatings do not represent a pH dependent dissolution polymethacrylate material. As there is no evidence which proves the contrary novelty (Art. 33(2) PCT) of the claimed subject-matter with respect to D1 and D2 is accepted.

The claimed subject-matter differs from the compositions disclosed in D3 in that in D3 not all particles are coated.

4. The problem of the pending application was to provide an oral pharmaceutical composition for the controlled release of an active agent in the intestinal tract. D4 is regarded to represent the closest prior art as it deals with the same problem, namely, the treatment of intestinal diseases. In one embodiment The composition comprises pellets coated with a first pH dependent release coating material which are filled into a capsule which is coated with a second pH dependent material. In contrast thereto the particles of the pending application are coated with the same pH dependent coating with different thicknesses. From D3 the skilled person learns that a coating made of a pH dependent material dissolves at the specific pH irrespective of the thickness of the coating. Therefore there is no suggestion in the prior art that the dissolution pH depends on the thickness of the coating made from a pH dissolution dependent polymethacrylate material.

US-A-4728512 discloses a pharmaceutical formulation comprising three groups of drug-releasing pellets presented in, for example, a capsule, of which each group of pellets releases the drug at a different time in the patient's digestive system. In particular, it discloses a formulation where one group of pellets is uncoated and releases the drug immediately upon release of the pellets from the capsule, a second group of pellets which have a pH-dependent coating (e.g. 20-30 wt% Eudragit S) and a third group of pellets which have a pH-independent coating, such as a dual-coat system where a time-dependent undercoat (e.g. hydroxypropyl methyl cellulose) is further coated with a hydratable diffusion barrier coating (e.g. Eudragit E30D and metallic stearate). The formulation thereby consists of three drug release systems which provide drug release maximums during the periods 0-2 hours from administration, 2-6 hours from administration and 4-10 hours from administration respectively. The formulation provides three doses of drug over a period of, for example, 12 hours, by releasing the drug on three occasions in an amount according to the relative quantity of each group of particles. The groups of particles are coated with different thicknesses of coating materials and therefore the document discloses the general concept of using different groups of particles with different release properties to release the active compound at different locations in the intestinal tract (by virtue of the different delay in releasing the drug from the second and third groups of pellets).

Both US-A-5260069 and US-A-5834024 disclose pharmaceutical compositions comprising at least two

pluralities of particles. The pluralities may be coated with different thicknesses of a coating material comprising a polymer blend. The blend comprises, as a major component, at least one water insoluble polymer and, as a minor component, a polymer whose solubility is dependent on pH. US-A-5260069 exemplifies compositions in which nifedipine and zidovudine are active components and US-A-5834024 exemplifies the use of diltiazem as the active component.

US-B-6267990 discloses a pharmaceutical composition comprising three pluralities of particles, one of which is uncoated and the other two are coated with different thicknesses of a pH dependent release coating material. US-B-6267990 exemplifies the use of the ACE inhibitor, captopril, as the active component.

US-A-5834021 exemplifies a pharmaceutical composition comprising a plurality of pellets comprising prednisolone metasulphobenzoate. The pellets are coated with a first pH dependent release coating material and then filled into a capsule which is then itself coated with a second pH dependent release coating material.

There is as yet no effective method or composition for controlling release of active compounds in the

CLAIMS

1. An oral pharmaceutical composition comprising two or more pluralities of particles, said particles comprising prednisolone metasulphobenzoate, wherein the particles of each said plurality are coated with a different thickness of a pH dissolution dependent polymethacrylate material to those of the or each other plurality, whereby prednisolone metasulphobenzoate is released at different locations in the intestinal tract.

2. A composition as claimed in Claim 1, wherein each of said pluralities of particles is coated with a different thickness of the polymethacrylate material, whereby prednisolone metasulphobenzoate is released at locations before and after the ileo-caecal valve.

3. A composition as claimed in Claim 1 or Claim 2, wherein the thickness of polymethacrylate material coating particles of each plurality of particles is of increments chosen to provide a homogeneous release profile of prednisolone metasulphobenzoate along at least one selected portion of the intestinal tract.

4. An oral pharmaceutical composition comprising two or more pluralities of particles, said particles comprising an active compound, wherein the particles of each said plurality are coated with a different thickness of a pH dissolution dependent polymethacrylate material to those of the or each other plurality, whereby the active compound is released at different locations in the intestinal tract.

5. A composition as claimed in Claim 4, wherein the active compound is selected from the group consisting of prednisolone metasulphobenzoate, metronidazole and alpha-amylase.

6. A composition as claimed in any of the preceding claims, wherein the particles of each plurality are coated with the same coating material as those of the or ~~each other plurality~~.

7. A composition as claimed in any of the preceding claims, wherein the polymethacrylate material comprises a methacrylic acid copolymer.

8. A composition as claimed in any of the preceding claims, wherein the polymethacrylate material comprises a copolymer of methacrylic acid and methyl methacrylate.

9. A composition as claimed in any of the preceding claims, wherein the polymethacrylate material is selected from a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:2, a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:1 or a mixture thereof.

10. A composition as claimed in any of the preceding claims, wherein the particles are coated with a methacrylic acid copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:2.

11. A composition as claimed in any of the preceding claims, wherein the particle has a diameter in the range 800 to 1500μm.

12. A composition as claimed in any of the preceding claims, wherein the particles are coated with the polymethacrylate material to a theoretical weight gain on coating in the range 5% to 30%.

13. A composition as claimed in any of the preceding claims, wherein the particles are coated with the polymethacrylate material to a theoretical weight gain on coating in the range 10% to 25%.

14. A composition as claimed in any of the preceding claims, wherein the thickness of polymethacrylate material coating particles of each plurality of particles is of increments chosen to provide a homogeneous release profile of the active compound along at least one selected portion of the intestinal tract.

15. A composition as claimed in any of the preceding claims, further comprising an enterically coated capsule within which the pluralities of particles are contained.

16. A composition as claimed in any of the preceding claims, wherein there are two pluralities of particles.

17. A composition as claimed in any of the preceding claims, wherein a first plurality of particles is coated to provide a theoretical weight gain of 15% and a second plurality of particles is coated to provide a theoretical weight gain of 20%.

18. A composition as claimed in Claim 16 and Claim 17, wherein the first and second pluralities of particles are present in a ratio of about 1:3.

19. Use of the coating thickness of a pH dissolution dependent coating material on particles comprising an active compound to control the release profile of the active compound in the intestinal tract.

20. A use as claimed in Claim 19, wherein the coating material is a polymethacrylate material.

21. A use as claimed in Claim 20, wherein the polymethacrylate material comprises a methacrylic acid copolymer.

22. A use as claimed in Claim 20 or Claim 21, wherein the polymethacrylate material comprises a copolymer of methacrylic acid and methyl methacrylate.

23. A use as claimed in any of Claims 19 to 22, wherein the polymethacrylate material is selected from a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:2, a copolymer of methacrylic acid and methyl methacrylate having a ratio of free carboxyl groups to ester groups of about 1:1 or a mixture thereof.

24. The use as claimed in any of Claims 19 to 23 wherein the active compound is selected from the group consisting of prednisolone metasulphobenzoate, metronidazole and alpha-amylase.

25. An oral composition as defined in any of Claims 1 to 18 for use in therapy or diagnosis practised on the human or animal body.

26. Use of a coating material selected from:

A. a polymethacrylate material; and

~~B. a pH dissolution dependent coating material~~

in the preparation of a medicament as defined in any of Claims 1 to 18 for the treatment of disorders of the intestinal tract.

27. A use as claimed in Claim 26, wherein the coating material is a polymethacrylate material.

28. A use as claimed in Claim 26 or Claim 27, wherein the coating material is a pH dissolution dependent polymethacrylate material.

29. Use of a polymethacrylate material in the preparation of a medicament as defined in any of Claims 1 to 18 for the treatment of Crohn's disease.

30. A method of treating a disorder of the intestinal tract of a patient, said method comprising administering to a patient an effective amount of an active compound for treating that disorder in at least two pluralities of particles each coated with a different thickness of a coating material selected from

A. polymethacrylate material; and

B. a pH dissolution dependent coating material

to release the active compound at locations in the intestinal tract at which symptoms of the disorder are displayed.

31. A method as claimed in Claim 30 wherein the disorder is Crohn's disease.

32. A method as claimed in Claim 30 or Claim 31 wherein there are two pluralities of particles.

33. A method as claimed in any of Claims 30 to 32 wherein the active compound is prednisolone metasulphobenzoate.

34. A method as claimed in any of Claims 30 to 33 wherein the coating material is polymethacrylate material.

35. A method as claimed in any of Claims 30 to 34 wherein the active compound is released at locations before and after the ileo-caecal valve.

36. A composition substantially as hereinbefore described with reference to the accompanying Examples.

37. A use of the coating thickness of a pH dissolution dependent coating material substantially as hereinbefore described with reference to the accompanying Examples.

38. A use of a coating material substantially as hereinbefore described with reference to the Examples.